IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Julie Straub, Howard Bernstein, Donald E. Checkering, III, Sarwat Khattak, and Greg Randall

Serial No.: 09/706,045 Art Unit: 1617

Filed: November 3, 2000 Examiner: E. Webman

For: *POROUS DRUG MATRICES AND METHODS OF MANUFACTURE THEREOF*

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 23-29 in the Office Action mailed October 15, 2003, in the above-identified patent application. A Notice of Appeal was filed on March 4, 2004. Submitted with this Appeal Brief is a Petition for Extension of Time to extend the period for response two months, to and including July 6, 2004. The Commissioner is hereby authorized to charge $375.00, the fee for the filing of this Appeal Brief for a small entity ($165.00), and the fee for a two-month extension of time for a small entity ($210), to Deposit Account No. 50-3129. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

Please note that the correspondence address for this application has changed. All future correspondence should be addressed as follows:

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(1) REAL PARTY IN INTEREST

The real party in interest of this application is Acusphere, Inc., the assignee.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 23-39 are pending and on appeal. Claims 1-22 have been cancelled.

(4) STATUS OF AMENDMENTS

An amendment after final rejection was filed on January 22, 2004. In the Advisory Action mailed February 18, 2004, the Examiner indicated that this amendment would be entered. An appendix sets forth the claims on appeal as amended.

(5) SUMMARY OF THE INVENTION

The claims define methods for delivering a drug to a patient in need thereof. The methods involve administering a therapeutically or prophylactically effective amount of the drug in a formulation containing a porous matrix (page 21, lines 27-30). The porous matrix contains a wetting agent and microparticles of the drug (originally filed claim 23). The porous matrix is in the form of a dry powder and has a TAP density less than or equal to 1.0 g/mL or has a total surface area of greater than or equal to 0.2 m^2/g (page 3, lines 12-14). The microparticles have a mean diameter between about 0.1 and 5 μm and a total surface area greater than about 0.5 m^2/mL (page 3, line 11 and originally filed claim 23). The mean diameter of the microparticles may be between about 0.5 and 5 μm (page 5, lines 28-30). The drug in the formulation may be a low aqueous solubility drug (page 6, lines 19-20). Alternatively, the drug may be a water soluble drug (page 11, line 22 until page 12, line 9).

The porous matrix is formed by the following process:

(1) dissolving the drug in a volatile solvent to form a drug solution,

(2) combining at least one volatile salt with the drug solution to form an emulsion, suspension or second solution,

(3) incorporating at least one wetting agent into the emulsion, suspension or second solution, and

(4) removing the volatile solvent and volatile salt from the emulsion, suspension or second solution to yield a porous matrix (page 3, lines 15-20, 24, and 28-30; and originally filed claim 18).

The formulation may be administered via parenteral, mucosal, oral, or topical administration (page 22, lines 1-3). When administered parenterally, the formulation may be administered via intravenous, intraarterial, intracardiac, intrathecal, intraosseous, intraarticular, intrasynovial, intracutaneous, subcutaneous, or intramuscular administration (page 22, lines 4-6). When mucosal administration is used, the formulation may be administered via pulmonary, buccal, sublingual, intranasal, rectal, or vaginal administration (page 22, lines 6-8) Alternatively, the formulation may be administered by intraocular, conjunctival, intracranial, intralesional, or intratumoral administration (page 22, lines 8-10). The formulation may be suspended in an aqueous solution suitable for parenteral administration (page 13, lines 7-10 and page 22, lines 11-14), in a tablet or capsule suitable for oral administration (page 22, lines 18-19), or in a suppository suitable for vaginal or rectal administration (page 22, lines 19-20).

(6) ISSUE ON APPEAL

The sole issue presented on appeal is whether claims 23-39 are novel as required by 35 U.S.C. § 102(e) over U.S. Patent No. 6,565,885 to Tarara *et al.* ("Tarara").

(7) GROUPING OF CLAIMS

The claims stand or fall together.

(8) ARGUMENTS

(i) Rejection Under 35 U.S.C. § 102

Tarara is not prior art under 35 U.S.C. § 102(e) in view of a Declaration under 37 C.F.R. § 1.131 by the inventors. Tarara also fails to disclose each claimed element. Accordingly, the claims are not anticipated by Tarara.

(a) Legal Standard under 35 U.S.C. § 102(e)

35 U.S.C. §102(e) prior art includes patents "granted on an application for patent by another filed in the United States *before the invention by the applicant* for patent" 35 U.S.C. §102 (e) (emphasis added). A declaration under may be used to "establish invention of the subject matter of the rejected claims prior to the effective date of the reference [...] on which the rejection is based." 37 C.F.R. § 1.131 (a). The declaration must show either (1) reduction to practice of the invention prior to the effective date of the reference or (2) conception of the invention prior to the effective date, coupled with due diligence from the effective date until a subsequent reduction to practice or the filing of the application. Chisum on Patents §3.08[1]. When a reference shows only part of the invention, such as a species within a generic invention, a Rule 131 affidavit is sufficient if it shows that the affiant had prior possession of that part of the invention disclosed by the reference. Chisum on Patents §3.08[1][b]. *In re Stempel*, 241 F.2d 755, 113 U.S.P.Q. 77 (C.C.P.A. 1957), the leading case on prior possession of part of an invention, explained that a reference "is valid only for what it discloses [therefore] if the application establishes priority with respect to that disclosure, and there is no statutory bar [the reference] is of no effect at al." 241 F.2d at 759-60. Therefore, a declaration under 37 C.F.R. § 1.131 is only required to antedate what is disclosed by the reference.

(b) Tarara is not available as prior art under 35 U.S.C. § 102 (e)

Tarara claims priority to a provisional application filed on September 29, 1997. Tarara discloses using a spray drying feedstock which contains a bioactive agent, surfactant, and a blowing agent, optionally with an excipient (abstract; col. 17, lines 11-16). Tarara defines

"bioactive agent" as "a substance which is used in connection with an application that is therapeutic or diagnostic in nature." (col. 6, lines 30-32). Some of Tarara's preferred embodiments also contain synthetic or natural polymers (see col. 11, line 63 until col. 12, line16).

A declaration under 37 C.F.R. § 1.131 executed by Julie Straub and Howard Bernstein on January 22, 2004 was submitted to remove Tarara as prior art. A copy is enclosed for the convenience of the Appeal Board. As demonstrated by this declaration, prior to September 29, 1997, applicants had conceived of and reduced to practice forming diagnostic particles using a spray drying feedstock which contains a bioactive agent, surfactant, and blowing agent. Therefore, Tarara is not available as prior art under 35 U.S.C. § 102(e).

In their declaration, Julie Straub and Howard Bernstein state that prior to September 29, 1997 they conceived of and reduced to practice compositions that are formed by spray drying a diagnostic agent with a surfactant and a blowing agent. As noted in the copies of the laboratory notebook pages attached to the Declaration (Exhibit A), microparticles containing air as the diagnostic agent were formed by spray drying (see page 14). Air bubbles were encapsulated in synthetic polymer microparticles by a spray drying process. The feed stock to the spray drying apparatus included a blowing agent (ammonium acetate), a surfactant (lecithin), polymers (poly(ethylene glycol)-co-poly(lactide-co-glycolide) (75:25) and D,L-poly(lactide)), and a diagnostic agent (air). This composition was homogenized to form an emulsion, which was then spray dried using a small-scale lab spray dryer. The resulting microparticles were echogenic (see page 105, injection 7).

Tarara defines "blowing agent" as "any volatile substance, which can be incorporated into the feed solution for the purpose of producing a perforated foam-like structure in the resulting dry microspheres." (col. 19, lines 26-29). Tarara specifically lists "[d]issolved or dispersed salts or organic substances which can be removed under reduced pressure by sublimation in a post-production step, such as ammonium salts, camphor, etc." (col. 19, lines 52-55). Thus ammonium acetate is a representative species of the genus of blowing agents disclosed in Tarara.

Tarara defines "bioactive agent" as "a substance which is used in connection with an application that is therapeutic or diagnostic in nature." (col. 6, lines 30-32). Tarara explains that "those skilled in the art will appreciate that any therapeutic or diagnostic agent may be incorporated in the stabilized dispersions." (col. 6, lines 35-37) Air is a gas used in echogenic particles for ultrasound imaging techniques (see e.g. Appendix A, page 105, injection 7). Thus, air is a representative species of the genus of bioactive agents disclosed in Tarara.

Tarara defines "surfactants" as "any compound or composition that aids in the formation of perforated microparticles or provides enhanced suspension stability, improved powder dispersibility or decreased particle aggregation." (col. 10, lines 14-18) Tarara specifically mentions lecithin as a typical surfactant (see col. 31, line 57). Thus, lecithin is a representative species of the genus of surfactants disclosed in Tarara.

Thus, the declaration shows that prior to Tarara's earliest priority date, applicants had conceived of and reduced to practice the subject matter disclosed by Tarara, namely a feed stock that contains a bioactive agent, a surfactant and a blowing agent, which is spray dried to form

porous particles containing the bioactive agent. Therefore, Tarara is not available as prior art under 35 U.S.C §102(e).

(c) Tarara does not disclose every element of the claimed methods

Tarara does not disclose the method of making defined by claim 23. The examiner's position is that it is only the properties of the resulting material, not the method, which are relevant to the analysis of the claimed composition. While this is technically accurate, it is also true that the properties of the resulting composition are a direct result of the method of manufacture. Different methods will yield different products. The only method of manufacture disclosed by Tarara is described at col. 5, lines 3-58. The method does not include the step of forming an emulsion, suspension or *second* solution. There is only one solution made. Accordingly, when this is spray dried, it will not form a two phase porous matrix such as would be made using appellants' claimed method, which requires two phases (either two liquid or a liquid and solid phase). Therefore, even though there are some elements commonly disclosed, the resulting product will have a different structure.

(9) SUMMARY AND CONCLUSION

The declaration under 37 C.F.R. §1.131 shows that applicants conceived of and reduced to practice the composition disclosed by Tarara prior to September 29, 1997, Tarara's earliest priority date. Therefore Tarara is not available as prior art under 35 U.S.C. § 102(e). Further, even if Tarara was available as prior art, it does not disclose every element of the claimed method. Therefore Tarara does not anticipate claims 23-39. For the foregoing reasons,

U.S.S.N. 09/706,045
Filed: November 3, 2000
APPEAL BRIEF

Appellant submits that the claims 23-39 are patentable.

Respectfully submitted,

Rivka D. Monheit

Rivka D. Monheit
Reg. No. 48,731

Date: July 6, 2004

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Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, July 6, 2004, to the Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450.

Gloria Miller

Date: July 6, 2004

Appendix: Claims On Appeal

Claims 1-22 (canceled).

23. (Previously Presented) A method of delivering a drug to a patient in need thereof, comprising

administering a therapeutically or prophylactically effective amount of the drug in a formulation comprising a porous matrix which comprises a wetting agent and microparticles of the drug, wherein the microparticles have a mean diameter between about 0.1 and 5 μm and a total surface area greater than about 0.5 m^2/mL, and wherein the porous matrix has a TAP density less than or equal to 1.0 g/mL or has a total surface area of greater than or equal to 0.2 m^2/g and is in the form of a dry powder, and

wherein the porous matrix is made by a process comprising

dissolving the drug in a volatile solvent to form a drug solution,

combining at least one volatile salt with the drug solution to form an emulsion, suspension, or second solution,

incorporating at least one wetting agent into the emulsion, suspension, or second solution, and

removing the volatile solvent and volatile salt from the emulsion, suspension, or second solution to yield the porous matrix.

24. (Previously Presented) The method of claim 23 wherein the formulation is administered by a route selected from the group consisting of parenteral, mucosal, oral, and topical administration.

25. (Previously Presented) The method of claim 24 wherein the parenteral route is selected from the group consisting of intravenous, intraarterial, intracardiac, intrathecal, intraosseous, intraarticular, intrasynovial, intracutaneous, subcutaneous, and intramuscular administration.

26. (Original) The method of claim 24 wherein the mucosal route is selected from the group consisting of pulmonary, buccal, sublingual, intranasal, rectal, and vaginal administration.

27. (Previously Presented) The method of claim 23 wherein the formulation is administered by intraocular or conjunctival administration.

28. (Previously Presented) The method of claim 23 wherein the formulation is administered by intracranial, intralesional, or intratumoral administration.

29. (Previously Presented) The method of claim 23 wherein the formulation is suspended in an aqueous solution suitable for parenteral administration.

30. (Original) The method of claim 23 wherein the formulation is in a tablet or capsule suitable for oral administration.

31. (Original) The method of claim 23 wherein the formulation is in a suppository suitable for vaginal or rectal administration.

32. (Previously Presented) The method of claim 23 wherein the formulation is administered by pulmonary administration.

33. (Previously Presented) The method of claim 23 wherein the dry powder form of the porous matrix has a TAP density less than or equal to 1.0 g/mL.

34. (Previously Presented) The method of claim 23 wherein the dry powder form of the porous matrix has a total surface area of greater than or equal to 0.2 m^2/g.

35. (Previously Presented) The method of claim 23 wherein the mean diameter of the microparticles is between about 0.5 and 5 μm.

36. (Previously Presented) The method of claim 23 wherein the drug is a low aqueous solubility drug.

37. (Previously Presented) The method of claim 36 wherein the drug is selected from the group consisting of albuterol, adapalene, doxazosin mesylate, mometasone furoate, ursodiol, amphotericin, enalapril maleate, felodipine, nefazodone hydrochloride, valrubicin, albendazole, conjugated estrogens, medroxyprogesterone acetate, nicardipine hydrochloride, zolpidem tartrate, amlodipine besylate, ethinyl estradiol, omeprazole, rubitecan, amlodipine besylate/ benazepril hydrochloride, etodolac, paroxetine hydrochloride, paclitaxel, atovaquone, felodipine, podofilox, paricalcitol, betamethasone dipropionate, fentanyl, pramipexole dihydrochloride, Vitamin D_3, finasteride, quetiapine fumarate, alprostadil, candesartan, cilexetil, fluconazole, ritonavir, busulfan, carbamazepine, flumazenil, risperidone, carbemazepine, carbidopa/ levodopa, ganciclovir, saquinavir, amprenavir, carboplatin, glyburide, sertraline hydrochloride, rofecoxib, carvedilol, halobetasol proprionate, sildenafil citrate, celecoxib, chlorthalidone, imiquimod, simvastatin, citalopram, ciprofloxacin, irinotecan hydrochloride, sparfloxacin, efavirenz, cisapride monohydrate, lansoprazole, tamsulosin hydrochloride, mofafinil, azithromycin, clarithromycin, letrozole, terbinafine hydrochloride, rosiglitazone maleate, diclofenac sodium, lomefloxacin hydrochloride, tirofiban hydrochloride, telmisartan, diazapam,

loratadine, toremifene citrate, thalidomide, dinoprostone, mefloquine hydrochloride, trandolapril, docetaxel, mitoxantrone hydrochloride, tretinoin, etodolac, triamcinolone acetate, estradiol, ursodiol, nelfinavir mesylate, indinavir, beclomethasone dipropionate, oxaprozin, flutamide, famotidine, nifedipine, prednisone, cefuroxime, lorazepam, digoxin, lovastatin, griseofulvin, naproxen, ibuprofen, isotretinoin, tamoxifen citrate, nimodipine, amiodarone, and alprazolam.

38. (Previously Presented) The method of claim 23 wherein the drug is a water soluble drug.

39. (Previously Presented) The method of claim 38 wherein the drug is selected from the group consisting of ceftriaxone, ketoconazole, ceftazidime, oxaprozin, valacyclovir, urofollitropin, famciclovir, flutamide, enalapril, mefformin, itraconazole, buspirone, gabapentin, fosinopril, tramadol, acarbose, lorazepan, follitropin, glipizide, omeprazole, fluoxetine, lisinopril, levofloxacin, zafirlukast, interferon, growth hormone, interleukin, erythropoietin, granulocyte stimulating factor, nizatidine, bupropion, perindopril, erbumine, adenosine, alendronate, alprostadil, benazepril, betaxolol, bleomycin sulfate, dexfenfluramine, diltiazem, fentanyl, flecainid, gemcitabine, glatiramer acetate, granisetron, lamivudine, mangafodipir trisodium, mesalamine, metoprolol fumarate, metronidazole, miglitol, moexipril, monteleukast, octreotide acetate, olopatadine, paricalcitol, somatropin, sumatriptan succinate, tacrine, verapamil, nabumetone, trovafloxacin, dolasetron, zidovudine, finasteride, tobramycin, isradipine, tolcapone, enoxaparin, fluconazole, lansoprazole, terbinafine, pamidronate, didanosine, diclofenac, cisapride, venlafaxine, troglitazone, fluvastatin, losartan, imiglucerase, donepezil, olanzapine, valsartan, fexofenadine, calcitonin, and ipratropium.

TABLE OF CONTENTS

Exhibit A

14 **TITLE** **PROJECT NO.**

Work continued from Page 13 [illegible] 8/29/95 **BOOK NO.** [redacted]

Investigator(s): H. Brook Date: [redacted]
Notebook/page #: Microsphere lot #: 943191-11

Microsphere Production

Process Room Conditions

Room Temp.:	22°C
Room Humidity:	56% RH

Polymer Preparation

Polymer type 1:	PEG-PLGA
Source & Lot no.:	BPI Lot # 504-14-19
Mass (g):	3.60 g
Polymer type 2:	DL-PLA
Source & Lot no.:	BI Lot # 34038
Mass (g):	3.61 g
Solvent Type:	MeCl2
Source & Lot no.:	EM lot no. 35068
Volume:	[illegible]
Surfactant type:	Lecithin
Surf. (Wt/Vol):	75 mg
Dissolution Meth.:	[illegible]
Dissolution Temp.:	Room temperature
Dissolution Time:	[illegible]
Excipient 1:	H_2O
Source & Lot no.:	[illegible] DI
Amount, g/mL:	[illegible]

Comments:
Dissolve ammonium acetate in water as follows:
1.08 g in [illegible] of H. D. Add [illegible] to polymer solution.

Aeration Methodology

Sonication:	None
Horn type:	
Frequency:	
Power:	
Temperature:	
Time:	
Time until spray:	
Sparging:	None
Gas type:	
Gas pressure:	
Temperature:	
Time:	
Time until spray:	
Homogenization:	VIRTIS
Blade type:	micro ultra-fine generator
Time:	[illegible]
Speed:	[illegible]
Temperature:	[illegible]
Time until spray:	~ [illegible] minutes

Comments:

Spray Conditions

Cleaning Proc.:	[illegible]		
Nozzle type:	0.7 mm standard [illegible]		
Gas Pressure:	95 psi		
Gas Flow rate:	400 L/h		
Gas type:	N_2 medical grade		
Feed Flowrate:	11 [illegible]		
Inlet Temp.:	50°C		
Start Time:	1:16		
Finish Time:	1:28		
Mass Recovered:	[illegible] = 1.97		
Yield (%):	27%		
Process Conditions:			
	Start 1:17	Middle 1:2?	Finish
Outlet Temp.:	29°C	30°C	29°C
Filter Vacuum:	-40 [illegible]	-[illegible]	-[illegible]

Comments:
Did not [illegible] inlet tube as I had done w/ a previous batch.

Drying Methodology

Type:	Lyophilization, VIRTIS [illegible]
Total dry time:	[illegible]
Mass recovered:	[illegible] 18.455 - [illegible] = 1.73 g
Yield (%):	[illegible] 25%

Comments:
[illegible]

Sizing Methodology

Room Temp.:	
Room Humidity:	
Screening Time:	
Screen size:	
Screen type:	
Product recovered:	
Yield (%):	

Comments:

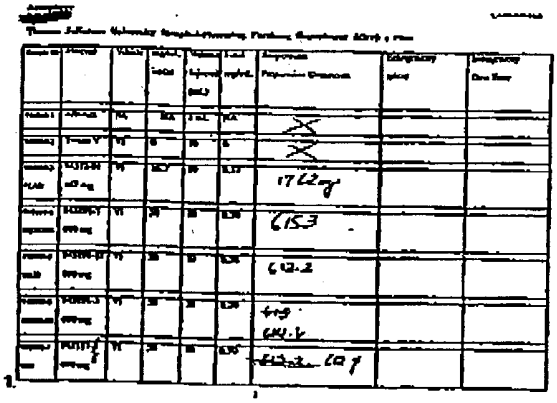
[illegible] [redacted]

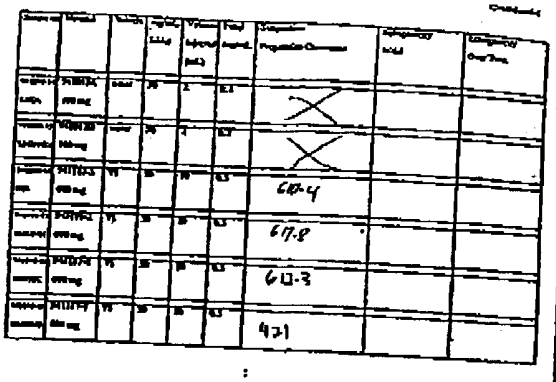
Work continued to Page 15

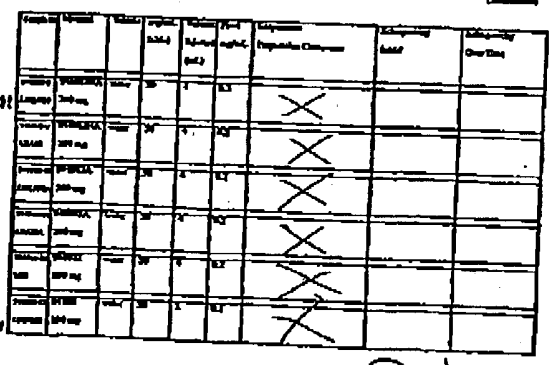
SIGNATURE [illegible] DATE [redacted]

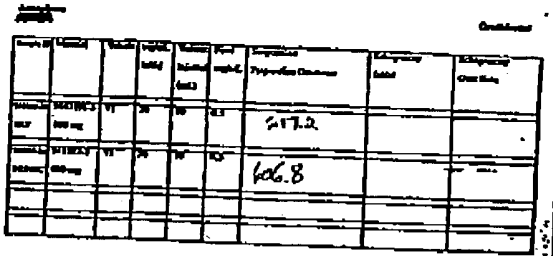
DISCLOSED TO AND UNDERSTOOD BY [illegible] DATE [redacted] WITNESS DATE [illegible]

80 TITLE TJU Study For [redacted] PROJECT NO









Samples weighed by Howard in Dry Box on [redacted]. All but the 941082 and 941083 samples sent to Roseberg on [redacted] by Airborne on dry ice / gel pak

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DATE [redacted] WITNESS

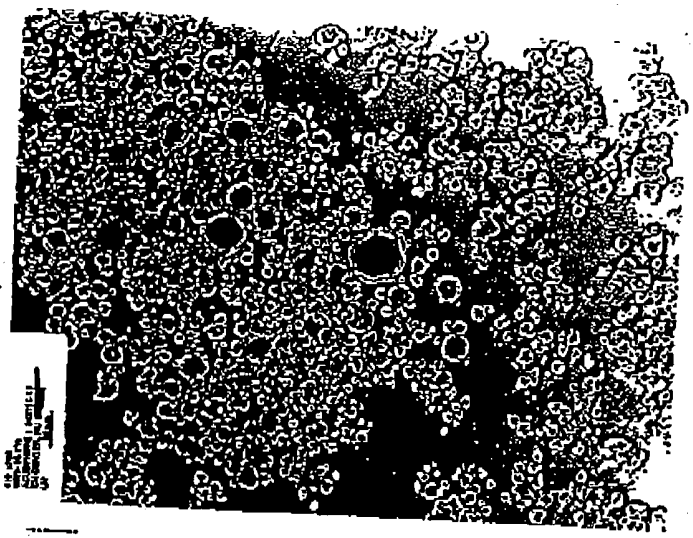
Work continued to Page 8 / 05

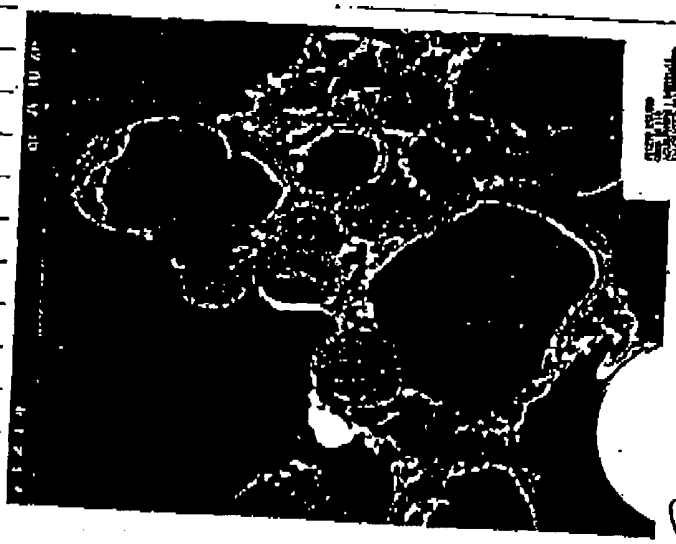
DATE [redacted]

DATE [redacted]

116

115





SCIENTIFIC ENERGY PRODUCTIONS CHICAGO 60640 Made in USA

SIGNATURE

Work continued to Page 117

DISCLOSED TO AND UNDERSTOOD BY

DATE

WITNESS

DATE

DATE

106 TITLE PROJECT NO

Notes

All samples will be prepared by vortexing and sonication.

All samples will be pre-weighed in 20 mL scintillation vials. Empty 20 mL scintillation vials will be brought.

Saline (0.9%) will be used instead of water for the bath, diluent, in the preparation of HCl. Pre-weighed samples of 14.2 g of NaCl will be brought out, and stored in 1000 mL vials in a bottle. Two such bottles will be sent to TTU. A total of 20 NaCl vials will be brought.

Vehicle 1 = 0.9% Tween 20, 2% glycerol ← never used

Vehicle 2 = 0.9% PEG, 5% EtOH, sonicated

1) System assembly same as [redacted] experiment, except 500mL Saline in baby
2) Vehicle 2 (VF) was used
3) Upon We did the entire study
4) After injection of sample, sample was stirred, flow rate was then increased to 500-800mL/min until echogenic material detected by the oscilloscope, Flow rate then dropped to 100-200 mL/min.
5) The "later window" moved dramatically with each pulse
6) Tubing was manipulated to remove bubbles. At least one (prior to injection 9) this resulted in change of alignment. After that one detected time, the machine was realigned.
7) Cleaning procedure: (1) Water pumped to remove all material, then saline pumped in (2) System pumped dry, saline pumped in (3) water pumped, saline pumped through.

(2) System pumped dry, saline pumped in

Work continued to Page

SIGNATURE

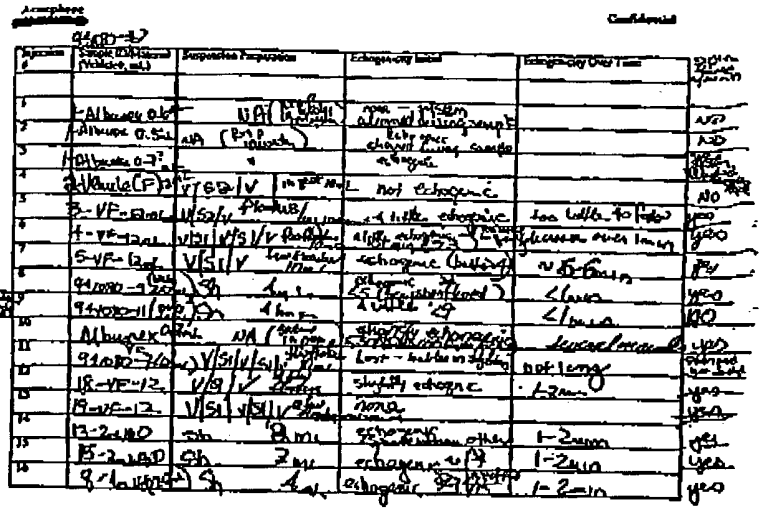
DISCLOSED TO AND UNDERSTOOD BY Henry T. Brick DATE [redacted] WITNESS

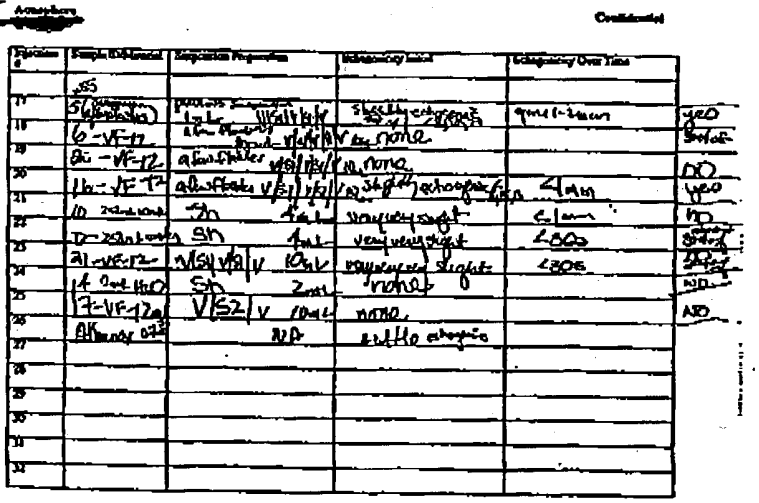
DATE [redacted]

TITLE:

Work ... 88/84-105

105





Study Rec'd 7/6 on [redacted]

SCIENTIFIC INDUSTRY PRODUCTIONS CHICAGO USA

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SIGNATURE

DISCLOSED TO AND UNDERSTOOD BY

DATE [redacted] WITNESS

DATE [redacted]

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